#14
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jacobus M. LEMMENS *et al.*	:	Examiner: S. GOLLAMUDI
Serial No.:	09/938,816	:	Group: 1616
Filed:	August 27, 2001	:	
For:	PHARMACEUTICAL COMPOSITIONS COMPRISING AMLODIPINE MALEATE		

DECLARATION UNDER 37 C.F.R.§ 1.132

I, Ing. Arlette Vanderheijden, do hereby declare as follows:

1. I am a co-inventor in the above-identified U.S. patent application.
2. In 1995 I completed my Higher Laboratory Education (Hoger Laboratorium Onderwijs) studies at Hogeschool Heerlen[1], in Sittard, The Netherlands in Organic Chemistry. I earned the title, "Ing." which I believe is equivalent to a Bachelor of Science degree in the U.S.
3. In 1997 I became employed by Synthon BV, the assignee of the present application, and have remained so to the present. I am presently a project manager and part of my responsibilities includes studying amlodipine maleate pharmaceutical compositions.
4. I am aware that the Examiner has rejected all claims in the present application over Davison, U.S. Patent 4,879,303, in combination with several other patents. I further understand that the Examiner's position is that Davison teaches pharmaceutical compositions should have "a pH of close to that of blood (7.4)" in column 2 lines 28-29. It is my understanding that the Examiner requested a comparison with a composition having a pH of about 7.4.
5. Accordingly, the following experiments were carried out under my direct supervision and control.

   Six tablet blends (A-F) having the nominal composition as shown in Table 1 were compressed into tablets. The theoretical and the calculated/measured amounts for both the batch and tablet of each blend are set forth in Appendix 1.

[1] The School has since changed its name to Hogeschool Zuyd.

The tablet blends were made by the same methodology wherein the amlodipine maleate and all excipients except magnesium stearate were transferred to a free fall mixer and mixed for fifteen (15) minutes. Then the magnesium stearate was added and the blend was mixed for another three (3) minutes. A sample from each blend was removed and the pH in a 20 wt% aqueous slurry was determined.

Table 1

	Blend A (mg)	Blend B (mg)	Blend C (mg)	Blend D (mg)	Blend E (mg)	Blend F (mg)
pH	7.2	6.36	6.07	5.95	5.8	5.19
Amlodipine Maleate	6.42	6.42	6.42	6.42	6.42	6.42
Microcystalline Cellulose	124.18	124.48	124.56	124.58	124.43	123.855
CalciumhydrogenPhosphate Anhydrous	63.0	63.0	63.0	63.0	63.0	63.0
Sodium Starch Glycolate	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium Stearate	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium Oxide	0.4	0.1	0.02	-	-	-
Maleic Acid	-	-	-	-	0.15	0.725
Total	200	200	200	200	200	200

The blends were compressed into tablets of about 200 mg using 8 mm round punches in an EK0 excenter press. The compression force was about eight (8) kN. Samples of each tablet were stored for one month in a stability room under hot (60°C) or humid (40°C and 75% relative humidity) conditions in order to carry out an accelerated stability study. Additional samples were stored for one month at 4°C as a baseline. The tablets were placed in the stability room loaded in containers without closures, i.e. so-called "open dish." After storage for one month the tablets from the three storage conditions (two accelerated and one baseline) were analyzed by a validated HPLC method for various impurities. The difference in the averaged values for several impurities between the baseline storage and the accelerated storage are summarized in Tables 2A and 2B.

Table 2A

Difference in Impurities Between 40°C/75% RH and Baseline After 1 month, Open Dish

	A pH 7.2	B pH 6.36	C pH 6.07	D pH 5.95	E pH 5.8	F pH 5.19
Δ Aspartate[1]	5.11	1.55	0.30	0.07	0.06	0.05
Δ Amide[2]	0	0	0	0	0.04	0.13
Δ Pyridine[3]	0.09	0.05	0.03	0.05	0.10	0.13
Δ Total Impurities	5.68	1.73	0.4	0.19	0.25	0.42

1. amlodipine aspartate (Z#204)
2. amlodipine amide (Z#205)
2. amlo-pyridine (Z#202)

Table 2B

Difference in Impurities Between 60°C and Baseline After 1 month, Open Dish

	A pH 7.2	B pH 6.36	C pH 6.07	D pH 5.95	E pH 5.8	F pH 5.19
Δ Aspartate	0.13	0.13	0.13	0.11	0.07	0.04
Δ Amide	0.11	0.11	0.10	0.08	0.41	0.85
Δ Pyridine	0.21	0.24	0.23	0.22	0.31	0.40
Δ Total Impurities	0.52	0.56	0.55	0.47	0.92	1.56

6. The data shows that compositions having a pH greater than 7 (e.g. tablet A) or less than 5.5 (e.g. tablet F) are more susceptible to increases in impurity during storage. Under warm and humid conditions the formation of aspartate is most pronounced in tablet A having a pH of 7.2. The total impurities are also highest in tablet A in comparison to the other tablets stored under the same conditions. Under hot conditions, the formation of the amide and pyridine impurities is highest in tablet F which has a pH of 5.19. Thus, the most robust tablets are between pH 5.5 to 7.

7. That tablets in this pH range would exhibit more favorable stability is unexpected over the prior Davison disclosure. Indeed, following the Examiner's

understanding, the pH of 7.2 should have provided good stability because it was close to that of blood. However, under warm and humid conditions, such a tablet exhibits the worst stability. Moreover, because Davison does not recognize the aspartate impurity nor that its mechanism of formation involves a Michael addition, there is no basis in Davison to predict that a pH of less than 7 would improve stability against aspartate formation. Accordingly, the above data shows unexpectedly superior results for the invention of the present application.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true and further that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

A Vanderheijden — 03.09.2003

Ing. Arlette Vanderheijden — Date

Encl. Appendix 1

APPENDIX 1

Blend A	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH		**7.20**		
ADP.mal	1.605 g	6.42 mg	1.608 g	6.432 mg
Microcrystalline cellulose	31.045 g	124.18 mg	31.077 g	124.308 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.770 g	63.08 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.013 g	4.052 mg
Magnesium stearate	0.50 g	2.00 mg	0.499 g	1.996 mg
Magnesium oxide	0.100 g	0.40 mg	97.9 mg	0.3916 mg
Maleic acid	-	-	-	
Total	**50.00 g**	**200.00 mg**	**50.0649 g**	**200.2596 mg**

Blend B	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH		**6.36**		
ADP.mal	1.605 g	6.42 mg	1.605 g	6.42 mg
Microcrystalline cellulose	31.12 g	124.48 mg	31.10 g	124.40 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	0.986 g	3.944 mg
Magnesium stearate	0.50 g	2.00 mg	0.516 g	2.064 mg
Magnesium oxide	0.025 g	0.10 mg	26.5 mg	0.106 mg
Maleic acid	-	-	-	-
Total	**50.00 mg**	**200.00 mg**	**49.9835 g**	**199.934 mg**

Blend C	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH		**6.07**		
ADP.mal	1.605 g	6.42 mg	1.607 g	6.428 mg
Microcrystalline cellulose	31.14 g	124.56 mg	31.15 g	124.60 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.77 g	63.08 mg
Sodium starch glycolate	1.00 g	4.00 mg	0.99 g	3.96 mg
Magnesium stearate	0.50 g	2.00 mg	0.51 g	2.04 mg
Magnesium oxide	5.00 mg	0.02 mg	6.10 mg	0.0244 mg
Maleic acid	-	-	-	-
Total	**50.00 g**	**200.00 mg**	**50.0331 g**	**200.1324 mg**

Blend D	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.95**	
ADP.mal	1.605 g	6.42 mg	1.606 g	6.424 mg
Microcrystalline cellulose	31.145 g	124.58 mg	31.164 g	124.656 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.751 g	63.004 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.01 g	4.04 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	-	-	-	-
Total	**50.00 mg**	**200.00 mg**	**50.031 g**	**200.124 mg**

Blend E	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.80**	
ADP.mal	1.605 g	6.42 mg	1.605 g	6.42 mg
Microcrystalline cellulose	31.1075 g	124.43 mg	31.137 g	124.548 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.00 g	4.00 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	0.0375 g	0.15 mg	37.3 mg	0.1492 mg
Total	**50.00 g**	**200.00 mg**	**50.0293 g**	**200.1172 mg**

Blend F	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.19**	
ADP.mal	1.605 g	6.42 mg	1.612 g	6.448 mg
Microcrystalline cellulose	30.96375 g	123.855 mg	30.954 g	123.816 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.06 g	4.24 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	0.18125 g	0.725 mg	180.7 mg	0.7228 mg
Total	**50.00 g**	**200.00 mg**	**50.0567 mg**	**200.2268 mg**